Adenovirus Vaccine Restoration: Phase 1 Clinical Study

Presentation to
Armed Forces Epidemiological Board

Mr. William Howell
Program Manager, USAMRMC

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Outline

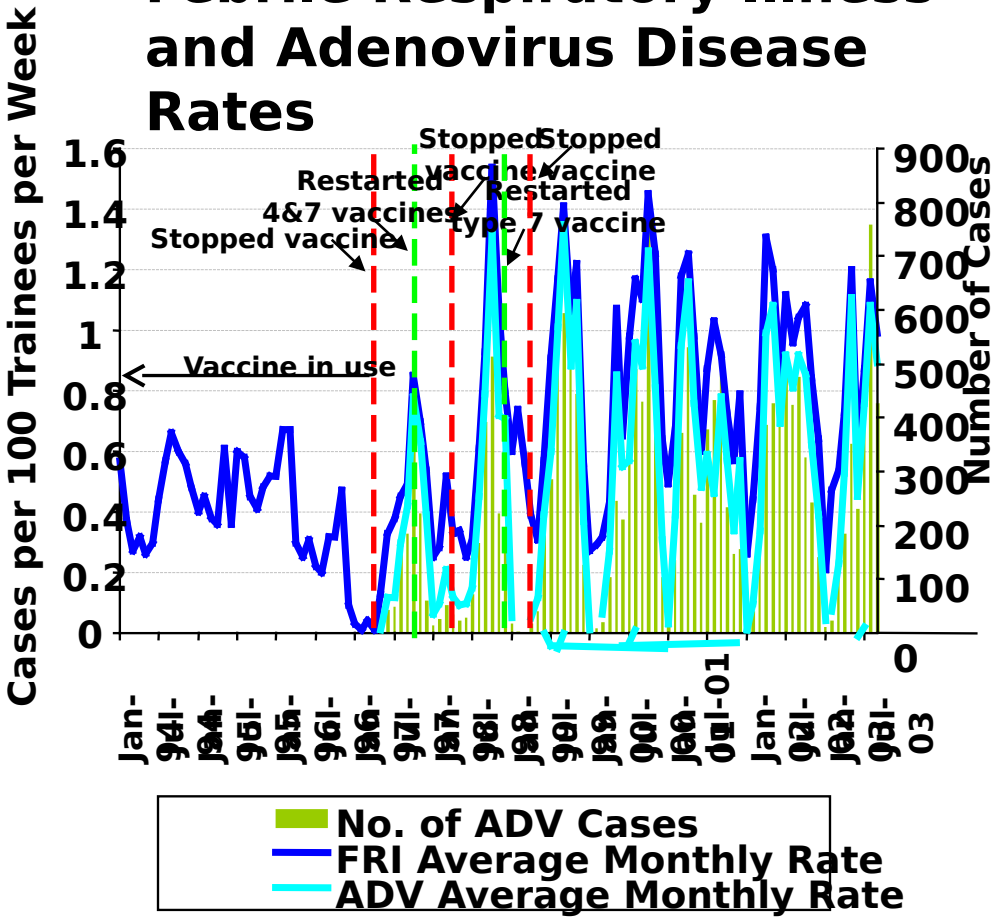
- Historical Review
- Vaccine Restoration Effort
- Phase 1 Clinical Study
- Summary

Adenovirus Vaccine

Historical Review

- ARD in troops: ’50s and ’60s
  - Adenovirus identified as significant contributor
- Adenovirus vaccine
  - Manufactured by Wyeth
  - Used in recruits since 1971
  - Manufacturing halted 1996
- AFEB Recommendations
- Institute of Medicine Recommendation
- Contract awarded in 2001 to Barr Labs to restore vaccine

Fort Jackson: Febrile Respiratory Illness and Adenovirus Disease Rates

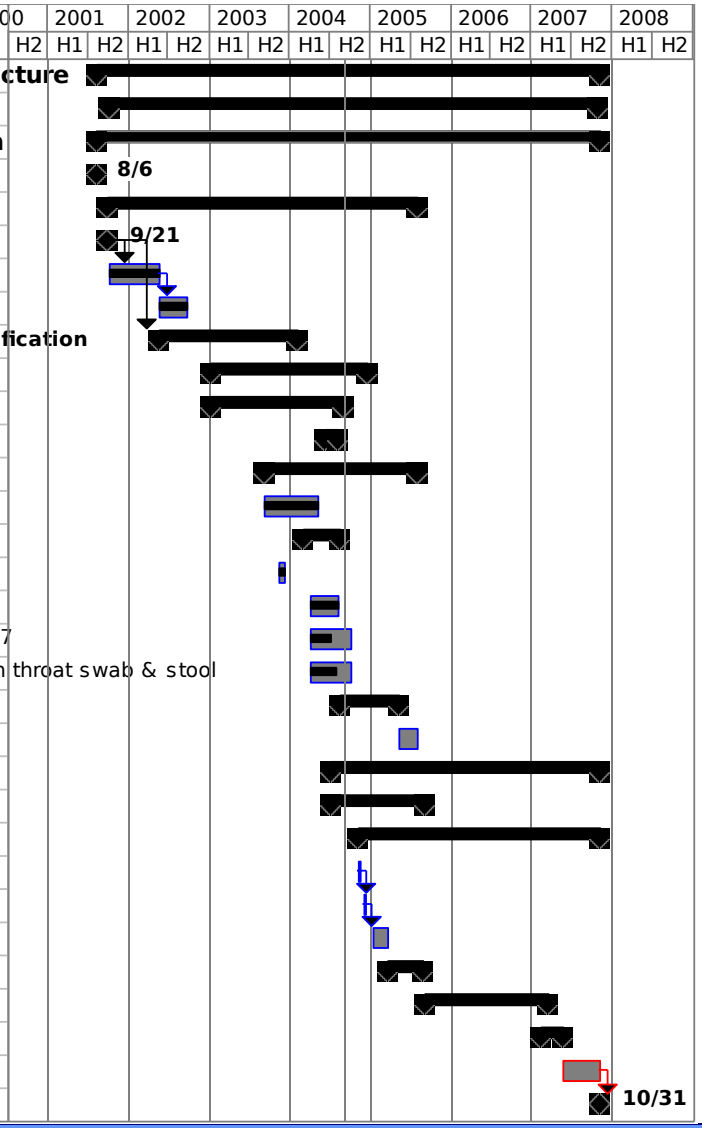


Adenovirus Vaccine Restoration Effort

Adenovirus Vaccine
Development Plan

Barr Laboratories
A subsidiary of Barr Pharmaceuticals, Inc.

ID	Task Name
1	**Adenovirus Type 4 & 7 Vaccine Development and Manufacture**
2	**COR Program Management**
224	**Adenovirus Barr Labs Baseline to Current Project Plan**
1	Adenovirus Vaccine, Types 4 & 7
2	**Basic Contract**
3	DoD Contract Award
4	Wyeth Technology and Material Transfer Agreement
5	Wyeth Material received
6	**Facility Construction, Equipment Installation and Qualification**
12	**Pilot and GMP Virus Production**
29	**IND Regulatory Activities**
36	**Seroprevalance Study**
40	**Phase I Clinical Trial**
41	Protocol Preparation
42	**Review and Approval**
49	HURC Protocol Review
50	Validation of microneut assay for volunteers
51	Validation of Taqman RT_PCR for quantitation of Adeno 4&7
52	Validation of isolation and identification assays ADV4&7 in throat swab & stool
53	**Perform Phase I Clinical**
59	Final Study Report
60	**Option 1**
61	**Vaccine Production for Phase II/III Clinical Trial**
65	**Phase II/III Clinical Trial**
66	Request FDA Meeting
67	Pre-Phase III FDA Meeting
68	Protocol Preparation
69	**Review and Approval**
75	**Phase II/III Clinical Study**
80	**Prepare and Submit BLA**
83	FDA Review
84	FDA Approval

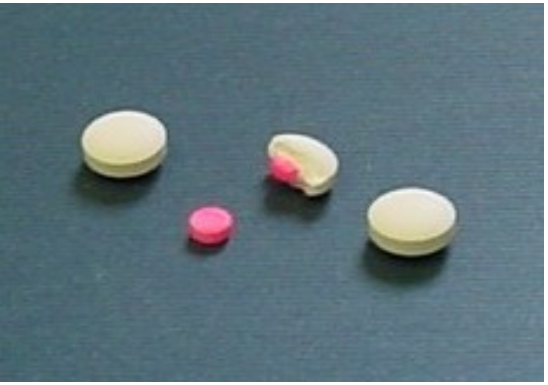


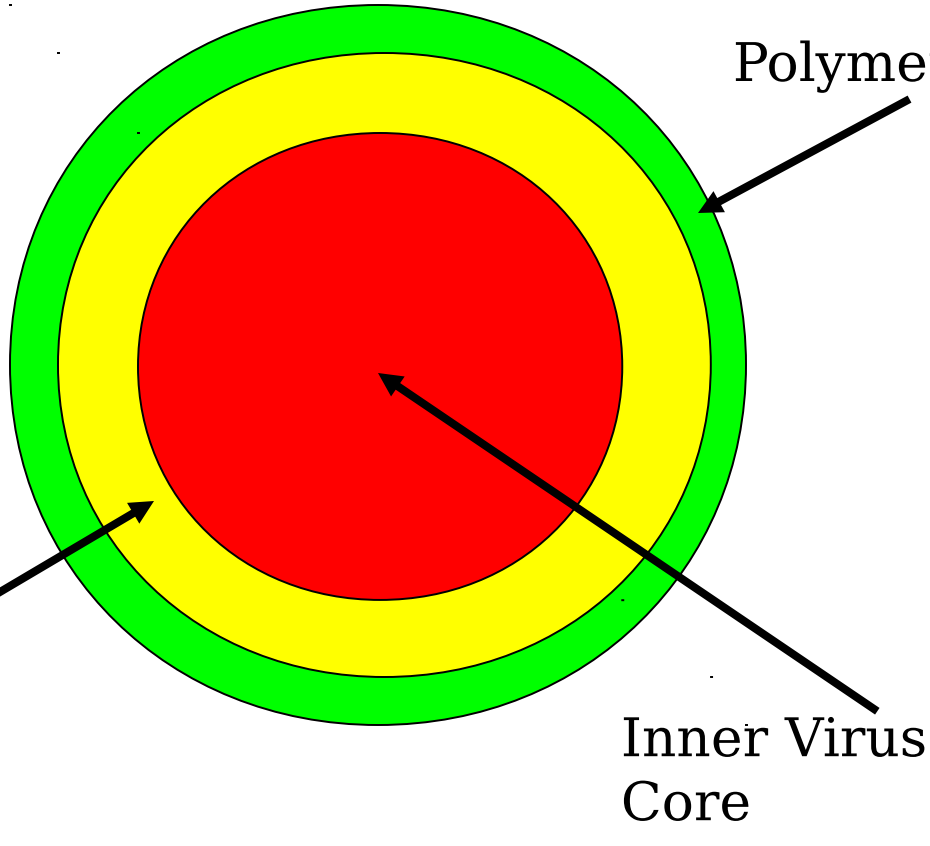
Restoration Strategy

- Replacement vaccine specifications will be as close to those of previously licensed vaccine as practical.
  - Contract proposal was based on limited public data, not detailed Wyeth information
  - Wyeth provided access to "*available*" manufacturing procedures and records
  - Barr/VaccGen worked to overcome gaps in records
  - FDA approval probably based upon efficacy but will approach immunogenicity as a basis

Adenovirus Vaccine

Adenovirus Vaccine Tablet





Provided by Dr. Andy Towle

Adenovirus Vaccine

Accomplishments:

- **IND submitted to FDA on 12 Jul 04**
- **BB-IND 11813 became active on 13 AUG 04**
- **Selected Fort Sam Houston, TX as the study site**
  - 91Ws, selected as population for study
  - Strong support from AMEDDC&S commander, BAMC commander, training brigade, battalion, and company commanders
- **WRAIR/Barr executed a sero-prevalence survey at FSH**
  - High sero-prevalence for both Adv 4 and Adv 7 in 91W (2% neg to both; 11% to type 4; 22% to type 7)
- **GMP Tablet manufacturing of Adenovirus vaccine Type 4 and Type 7 is complete for Phase I Clinical Trial**
  - All lot release tests completed
  - Stability testing on tablets
  - Product released 9 SEP 04
- **Screening of volunteers for Phase 1 began 14 AUG 04**

Clinical Development Stage

A Phase I, Randomized, Double-Blind, Placebo Controlled Study to Evaluate The Safety And Immunogenicity Of The Live, Oral Type-4 And Type-7 Adenovirus Vaccines

Phase I Study Objectives

Primary:

1. Evaluation of the safety of the type 4 and type 7 oral adenovirus vaccines administered together.

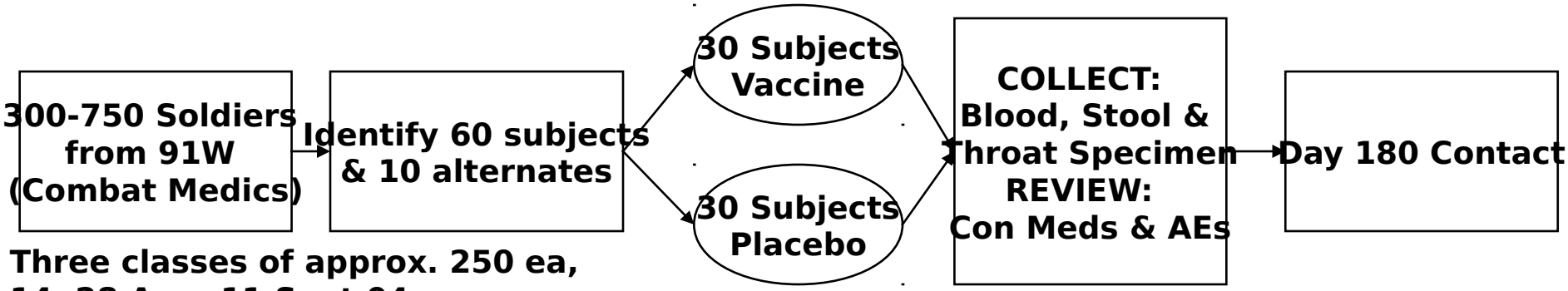
Secondary:

1. Evaluation of the immune response (neutralizing antibody titer and seroconversion rate) to the type 4 and the type 7 oral adenovirus vaccines.

2. Characterization of the duration of vaccine virus shedding in the stool and throat secretions in vaccine recipients.

Adenovirus Vaccine

Study Design



Three classes of approx. 250 ea, 14, 28 Aug, 11 Sept 04

SCREENING
Day –28

Need Serology Report

Staff
5 Lab Tech
45 Clinical Research Nurse (CRN)
5-7 AD MDs
1 Officer, 2 NCO's
3 Barr Floaters

RANDOMIZED
Day 0 Baseline
(25 SEP 04)

Staff
5 Lab Tech
5 CRN
3-5 AD MDs
1 Officer, 2 NCO's
1-3 Barr Floaters

F/U visits on Days 7, 14, 21, 28 & 56

Staff
PI
Lead CRN

Visit – Telephone or Letter

FDA Requirement

Adenovirus Vaccine

Screening

Photo provided by COL Longfield

- As of 28 Aug 04
  - Total of 212 subjects volunteered for screening
  - Preliminary reports on seroprevalence of ADV 4 & 7 in volunteers is similar to those of seroprevalence survey in July

Moving Forward

- Next 3 months
  - Modify manufacturing facility to include lyophilzation equipment
  - Produce additional bulk virus
  - Plan for FDA follow-up
    - Complete preclinical package
    - Begin discussions concerning “next” clinical trial

Moving Forward

- Next 6-9 months
  - Requalify manufacturing facility
  - Produce additional vaccine
  - Report on Phase I Clinical Trial
  - Plan for Phase III clinical trial
    - Finalize design
    - Coordinate site activities
    - Continue discussions concerning “next” clinical trial

Summary

- Adenovirus vaccine restoration program is on schedule to complete first clinical trial by Fall FY 2004

- Risks
  - Lower volunteer number than planned but still within range
  - High background from previous exposure to ADV (e.g. high seropositivity)

- Advantages
  - DoD, WRAIR and Barr/VaccGen are working synergistically
  - Problems to date have been dealt with successfully